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(54) **Pharmaceutical compositions for acne treatment**

(57) Pharmaceutical compositions useful in the treatment of acne comprising L-cysteine or a pharmaceutically acceptable salt thereof and an antibacterial agent such as propylene phenoxetol together with a pharmaceutically acceptable carrier.

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SPECIFICATION

## Pharmaceutical compositions

5 The present invention relates to pharmaceutical compositions useful in the treatment of acne which compositions comprise L-cysteine or a pharmaceutically acceptable salt thereof and propylene phenoxetol. 5

Anti-acne treatments are well known but none are sufficiently satisfactory as to obviate the need of a further method of treatment. Known methods of treatment by ultra-violet radiation, x-rays or surgery can cause tissue to be destroyed or the sebaceous glands to atrophy; conventional oestrogen therapy similarly atrophies the sebaceous glands and may additionally be unacceptable to female patients and may require a considerable time to have an effect; and treatment with benzoyl peroxide can cause local irritation. Clearly it would be desirable to offer an alternative method of treating acne. 10

10 The present invention is based upon the discovery that compositions containing L-cysteine and propylene phenoxetol may be used to treat acne without an unacceptable level of undesirable side effects such as the destruction of tissues to an unacceptable degree. 15

15 Accordingly, the present invention provides a pharmaceutical composition useful in the treatment of acne which composition comprises L-cysteine or a pharmaceutically acceptable salt thereof and propylene phenoxetol.

One of the considerable advantages of using cysteine in the treatment of acne is that the medical practitioner will be aware that it is a natural amino acid, so that confidence may be felt in that unconventional 20 and possibly irritant materials such as thioglycolic acid can be avoided (U.S. Patent No. 4107330 discloses the topical applications of thioglycolic acid in the treatment of acne). Organic sulphydryl and in particular N-acetyl cysteine have been applied to the skin in order to reduce sebum production (see U.K. Patent No. 1317773) but they were not shown to have any effect on acne. L-cysteine has been used in the 25 treatment of eye diseases (see German Published Patent Application No. 2441621) but that use is unrelated to the treatment of acne. 25

Propylene phenoxetol, 1-phenoxypyropan-2-ol, has been used in topical compositions for the treatment of skin bacterial infections and skin fungal infections. Its use, together with L-cysteine in the treatment of acne has not been disclosed or suggested.

30 The usefulness of L-cysteine and propylene phenoxetol in the treatment of acne is therefore particularly surprising.

The L-cysteine and propylene phenoxetol are normally applied in the form of a pharmaceutical composition which comprises L-cysteine or a pharmaceutically acceptable salt thereof and propylene phenoxetol and a pharmaceutically acceptable carrier therefor. The L-cysteine may have D-cysteine in association 35 therewith if desired but normally and preferably L-cysteine is employed free of D-cysteine. Any convenient composition may be employed as long as it is free of oxidising agents or other agents incompatible with L-cysteine or propylene phenoxetol. Compositions analogous to those of the aforementioned patent documents may be employed if desired. However it is preferred to employ a self-supporting aqueous gel. 35

Accordingly this invention provides a pharmaceutical composition adapted for topical administration in 40 the form of a self-supporting aqueous gel containing L-cysteine or a pharmaceutically acceptable salt thereof and propylene phenoxetol.

Acceptable salts of cysteine include those with topically acceptable metallic ions or nitrogenous bases or topically acceptable acids. A particularly apt salt is the hydrochloride. By a self-supporting gel is meant a gel which when applied to an area of skin remains in contact with the area.

45 Most suitably the composition of this invention will contain from 0.1 to 15% of L-cysteine or a pharmaceutically acceptable salt thereof, more favourably 2.0 to 12% and preferably from 4 to 8% (terms when used herein are expressed on a wt./wt. basis). 45

Most suitably the composition of this invention will contain from 0.1 to 5% of propylene phenoxetol, 1-phenoxypyropan-2-ol, more favourably 1 to 4%, and preferably from 1.5 to 3%, for example 2%. 50

50 Optionally, though not preferred, the composition of this invention will contain preservative. Preservatives which are most apt are those commonly used in pharmaceutical compositions. Preferably the preservative will be benzoic acid, in an amount of 0.01 to 0.5% preferably 0.05 to 0.2%. 50

Normally and preferably the composition will contain a pharmaceutically acceptable gelling agent such as cellulose derivatives or gums or starches or alginates and polymers such as polyvinyl pyrrolidone or 55 polyvinyl alcohol or polyethoxy-polypropoxy glycol copolymers, but a preferred gelling agent is a polyacrylic acid lightly cross-linked with triethyl sucrose. Such polymers are known as carboxyvinyl polymers of which the Carbopol (Trade Mark) are one commercial embodiment. To form gels these polymers must be neutralised. Suitable neutralising agents include solutions of alkali metal or ammonium hydroxide and nitrogenous bases. A preferred neutraliser is a solution of sodium hydroxide. 55

60 Suitably the pharmaceutical compositions of the present invention in the form of a gel will contain from 0.1 to 5% of gelling agent depending on the efficacy of the agent, more suitably 0.5 to 4% and preferably 1 to 3%, for example 1.5%, 2% or 2.5%. 60

Normally and preferably the composition will contain a humectant to prevent the gel drying in use. Such humectants include alkylene glycols. A particularly preferred humectant is propylene glycol. This 65 agent has the added advantage in easing the dispersion of the gelling agent in the bulk of the water 65

5 during preparation. Suitably the composition may contain from 2 to 10% of humectant and preferably 3 to 7%.

5 Most suitably the pH of the composition will be controlled to prevent oxidation of L-cysteine base to cystine which occurs readily in solutions having a pH value of greater than 8. The suitable range of pH value is from 2 to 8, most suitably from 3 to 6 and preferably 4 to 6.

10 The pH value of a gel composition may also depend upon the choice of gelling agent and the viscosity required for the final gel. Thus, if the pH value is at the higher end of the range a hydroxyethyl cellulose gelling agent may be used and for gels of lower pH the preferred gelling agent is a polyacrylic acid lightly cross-linked by triallyl sucrose, when for example pH values of 4.5 and 5.5 are employed.

15 The viscosity of the final gel were measured using a Ferranti-Shirley cone and plate viscometer using the following parameters.

4 cm cone  
120 second sweep time  
15 600g cm<sup>-1</sup> torque spring  
10 rpm speed  
25°C temperature

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20 The apparent viscosity at maximum shear (10 r.p.m. = 113.7 sec<sup>-1</sup>) is suitably between 30 and 80 poise and is preferably between 60 and 75 poise.

25 Optionally the compositions of the present invention may also contain other ingredients including perfumes and inert fillers such as titanium dioxide to provide a white rather than colourless gel.

30 Normally and preferably the water used in the composition will be freshly distilled water which has been de-oxygenated by boiling and allowed to cool with filtered 'inert' gas bubbling through it. By 'inert' gas is meant a non-oxidising gas for cysteine, for example carbon dioxide, particularly preferred as nitrogen. It is also envisaged that any type of water for example deionized water, may be used provided it is degassed to remove oxygen and maintained thereafter under nitrogen. L-cysteine and its salts are readily oxidised in aqueous solutions by oxygen dissolved in the water, hence removal of this oxygen and isolation of this solution from air, avoids oxidation of L-cysteine and its salts.

35 The particularly favoured form of the composition of the present invention comprises from 2 to 12% of L-cysteine hydrochloride, 1 to 4% of propylene phenoxetol, 2 to 10% propylene glycol, 0.1 to 5% polyacrylic acid cross-linked by triallyl sucrose, sodium hydroxide solution to give a pH of 5.4 and sufficient water to adjust the volume to 100%.

40 A preferred form of the composition of the present invention comprises from 4 to 8% of L-cysteine, 1.5 to 3% propylene phenoxetol, 5% propylene glycol, 1.5% polyacrylic acid lightly cross-linked with triallyl sucrose, sodium hydroxide solution to adjust the pH of 5.4 and sufficient water to adjust the volume to 100%.

45 Typically the composition of the present invention will be packed into araldite lacquered aluminium tubes.

50 40 In a second aspect therefore the invention provides a method of treating acne which comprises applying topically to the affected areas an effective amount of L-cysteine or a pharmaceutically acceptable salt thereof and propylene phenoxetol. The composition will be applied topically to the affected area 2 times daily or more frequently if required.

55 45 In severe cases it may be desirable to apply the composition to the affected area up to 6 times a day for example, 2, 3, 4, 5 or 6 times daily. Generally 2, 3 or 4 applications daily are most convenient and usually 2 or 3 applications will be made. In mild cases a single application per day may be envisaged. Generally, treatment will last for at least 7 days and may proceed for up to 14 to 28 days or even longer if a physician considers it desirable.

60 50 In view of the susceptibility of cysteine to oxidation, the skilled worker will be aware that the compositions employed will be free of agents that would oxidise the cysteine.

65 55 Although propylene phenoxetol is the preferred anti-bacterial agent in a less favoured aspect alternative anti-bacterial agents may be employed. Thus in a broader aspect the present invention provides a pharmaceutical composition useful in the treatment of acne which composition comprises L-cysteine or a pharmaceutically acceptable salt thereof and an anti-bacterial agent.

70 60 Aptly the composition will contain from 0.1 to 15% of L-cysteine or a pharmaceutically acceptable salt thereof. Suitably the composition will contain from 0.2 to 2.0% L-cysteine or a pharmaceutically acceptable salt thereof, more suitably will contain 0.25 to 1.5% and preferably 0.3 to 0.5%, for example 0.35%, 0.40% and 0.45% of L-cysteine or a pharmaceutically acceptable salt thereof. Preferably the hydrochloride of L-cysteine is employed.

75 65 The effectiveness of compositions containing such low concentrations of L-cysteine with the antibacterial agent is particularly surprising. Such concentrations have the added advantage of being particularly friendly towards the skin.

80 70 Apt anti-bacterial agents are those which are compatible with L-cysteine. Suitable anti-bacterial agents include quaternary ammonium salts, for example benzalkonium chloride and propylene phenoxetol. The preferred anti-bacterial agent is propylene phenoxetol.

The following Examples are illustrative of the invention.

*Example 1*

5 An aqueous gel was made containing:

L-cysteine	7.0% w/w	210g
Propylene phenoxetol	2.5% w/w	75g
Propylene glycol	4.5% w/w	135g
Carbopol 934P	2.0% w/w	60g

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Sodium hydroxide solution to adjust the pH to 5.4

Distilled water to adjust the volume to 100% w/w 2520g.

15 15 The freshly distilled water was boiled to remove dissolved oxygen and allowed to cool with filtered nitrogen bubbling through. Nitrogen was bubbled through the bulk of the composition for the entirety of the process including the filling. The Carbopol 934P was dissolved in the water by warming and stirring. Then the water was allowed to cool to ambient temperature. The propylene phenoxetol was dispersed in the propylene glycol and then added to the cool water with stirring. The L-cysteine was then dissolved in 20 the solution and the pH adjusted to pH 5.4 using sodium hydroxide solution. The weight of solution was adjusted to the weight required by addition of deoxygenated water. The resultant solution was mixed for a further 15 minutes under a nitrogen blanket. The resultant clear product was transferred to a tube filling apparatus under a blanket of nitrogen. The product was filled in a conventional manner into araldite lacquered aluminium tubes which have been flushed with nitrogen. The tubes were sealed immediately.

25 25 The gel was dispensed from the tube as required.

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*Example 2*

An aqueous gel was made containing:

L-cysteine	8.0%
Propylene phenoxetol	2.0%
Propylene glycol	7.0%
Carbopol 934P	1.25%
Titanium dioxide	0.25%
Perfume	0.05%

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Sodium hydroxide solution to adjust pH to 5.2

Distilled water to adjust the weight to 100%.

40 40 The gel was formed and packed using the methods described in Example 1. The titanium dioxide and perfume were added along with the propylene phenoxetol after first mixing with the propylene glycol.

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*Example 3*

An aqueous gel was made containing:

L-cysteine hydrochloride	10%
Propylene phenoxetol	2%
Propylene glycol	6%
Carbopol 934P	2%

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Sodium hydroxide solution to adjust the pH to 4.5

Distilled water to adjust the weight to 100g.

55 55 The gel was prepared and packaged in a similar manner to that described in Example 1.

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*Example 4*

An aqueous gel was prepared containing:

L-cysteine hydrochloride	0.45%
Propylene glycol	6.0%
Carbopol 934P	1.5%
Titanium dioxide	0.25%
Perfume	0.06%

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Sodium hydroxide solution to adjust the pH to 5.6

Distilled water to adjust the weight to 100g.

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The gel was formed in a similar manner to that described in Example 2.

An aqueous gel was prepared containing:  
5 L-cysteine 0.35%  
Propylene phenoxetol 2.0%  
Propylene glycol 7.0%  
Carbopol 934P 1.25%  
Perfume 0.05%

10 Sodium hydroxide solution to adjust the pH to 5.2  
Distilled water to adjust the weight to 100g.

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The gel was formed in a similar manner to that described in Example 1.

15 CLAIMS

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1. A pharmaceutical composition useful in the treatment of acne which composition comprises L-cysteine or a pharmaceutically acceptable salt thereof and propylene phenoxetol.
2. A composition as claimed in claim 1 which comprises from 0.1 to 15% of L-cysteine or a pharmaceutically acceptable salt thereof.
3. A composition as claimed in either of claims 1 or 2 which comprises from 0.1 to 5% of propylene phenoxetol.
4. A composition as claimed in any of claims 1 to 3 in which the composition is in the form of a self-supporting aqueous gel.
5. A composition as claimed in claim 4 in which the composition comprises from 0.1 to 5% of gelling agent.
6. A composition as claimed in claim 5 in which the gelling agent is polyacrylic acid lightly cross-linked with triallyl sucrose.
7. A composition as claimed in any of claims 4 to 6 which comprises from 2 to 10% of a humectant.
8. A composition as claimed in claim 7 in which the humectant is propylene glycol.
9. A composition as claimed in any of claims 1 to 8 in which the composition has a pH in the range 3 to 6.
10. A pharmaceutical composition useful in the treatment of acne which composition comprises L-cysteine or a pharmaceutically acceptable salt.
11. A pharmaceutical composition as claimed in either of claims 10 or 11 which contains from 0.1 to 5% of antibacterial agent.
12. A pharmaceutical composition as claimed in claim 12 in which the antibacterial agent is propylene phenoxetol.

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